Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 44, No. 7, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.06.066

# Cilostazol Inhibits Leukocyte Integrin Mac-1, Leading to a Potential Reduction in Restenosis After Coronary Stent Implantation

Teruo Inoue, MD, FACC,*† Toshihiko Uchida, MD,† Masashi Sakuma, MD,† Yoshitaka Imoto,‡ Yasushi Ozeki, PHD,§ Yukio Ozaki, MD,§ Yutaka Hikichi, MD,* Koichi Node, MD*

*Saga, Koshigaya, Tokyo, and Tamaho, Japan*

**OBJECTIVES** The aim of this study was to confirm clinically a hypothesis that cilostazol inhibits leukocyte Mac-1, leading to prevention of post-stent restenosis.

**BACKGROUND** The platelet phosphodiesterase III inhibitor called cilostazol also inhibits alpha-granule release of P-selectin in platelets. The P-selectin–mediated platelet-leukocyte interaction promotes activation and upregulation of leukocyte Mac-1 after coronary stenting, which plays a key role on the mechanism of restenosis. Thus, cilostazol's potential inhibition of this process may lead to prevention of restenosis.

**METHODS** Using flow cytometric analysis of whole blood obtained from the coronary sinus, the expression of platelet membrane glycoproteins and neutrophil adhesion molecules was observed in 70 consecutive patients undergoing coronary stenting. The patients were randomly assigned to either a cilostazol or ticlopidine group before stent placement.

**RESULTS** The restenosis rate was lower (15% vs. 31%, $p < 0.05$) in the cilostazol group ($n = 34$) than in the ticlopidine group ($n = 32$). A stent-induced increase in platelet P-selectin (CD62P) expression and an increase in neutrophil Mac-1 (CD11b) expression were suppressed in the cilostazol group compared with the ticlopidine group. Angiographic late lumen loss was correlated with the relative changes in platelet P-selectin and neutrophil Mac-1 at 48 h after coronary stenting.

**CONCLUSIONS** Cilostazol may have effects on suppression of P-selectin–mediated platelet activation, platelet-leukocyte interaction, and subsequent Mac-1–mediated leukocyte activation, which might lead to a reduced restenosis rate after coronary stent implantation. (J Am Coll Cardiol 2004;44:1408–14) © 2004 by the American College of Cardiology Foundation

Cilostazol (6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2[1H]-quinolinone) is an antiplatelet drug (1) developed in Japan, which has been applied as part of an antiplatelet regimen after coronary stenting. Its antiplatelet action is mainly due to phosphodiesterase (PDE) III inhibition, which also results in reduced smooth muscle cell growth and extracellular matrix synthesis (2,3), and these additional effects might be expected to reduce post-stent restenosis. Indeed, several clinical trials, including our own randomized trial, have provided data that cilostazol can lower the restenosis rate (4). However, most of these trials were done in the setting of a single-center trial with a small sample size. More recently, a larger cohort U.S. multicenter study—the Cilostazol for REStenosis Trial (CREST) (5)—concluded that cilostazol significantly reduced the rate of restenosis after coronary stenting. In addition to the antiplatelet action due to PDE III inhibition, cilostazol also inhibits activation-dependent alpha-granule release and P-selectin expression on the surface of platelets (6), and the clinical significance still needs to be clarified in detail.

The activation of leukocytes, neutrophils, and monocytes, as well as their interaction with platelets mediated by cell adhesion molecules, are known to play an important causative role in the development of restenosis after percutaneous coronary intervention (PCI) (7–10). Among various adhesion molecules, leukocyte integrin, Mac-1 (CD11b/CD18), is considered to be one of the key proteins in the mechanism of restenosis. Clinical evidence indicates that PCI results in activation and upregulation of Mac-1 on the surface of neutrophils in association with restenosis (10–15). In experimental models, Mac-1 blockade (16) or the absence of Mac-1 (17) suppressed neointimal thickening after PCI. There is increasing evidence that the interaction between platelets and leukocytes across an adherent layer of platelets precedes diapedesis and the infiltration of inflammatory cells into the PCI-induced injured vessel wall, which is denuded of vascular endothelial cells by balloon inflation (18–20). Platelet surface P-selectin mediates the rolling attachment of leukocytes with the platelet layer (21,22). Furthermore, Mac-1 is of particular importance in the process of transplatelet migration and firm adhesion of leukocytes. In the process of the platelet-leukocyte interaction, an adhesion cascade appears to occur with considerable cross-talk between P-selectin and Mac-1 (20,21). Thus, we hypothesize that cilostazol's inhibitory effects on P-selectin–

From the *Department of Cardiovascular and Renal Medicine, Saga University Faculty of Medicine, Saga; †Department of Cardiology, Koshigaya Hospital, Dokkyo University School of Medicine, Koshigaya; ‡Yufu Itonaga Company, Tokyo; and §Department of Laboratory Medicine, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Tamaho, Japan. This study was supported in part by a grant from the Vehicle Racing Commemorative Foundation, Tokyo, Japan.

Manuscript received May 12, 2004; revised manuscript received June 23, 2004, accepted June 29, 2004.

**Abbreviations and Acronyms**

cAMP = cyclic adenosine monophosphate
CREST = Cilostazol for REStenosis Trial
DMSO = dimethyl sulfoxide
FITC = fluorescein isothiocyanate
FMLP = formyl-methyonyl leucyl phenylalanine
MFI = mean channel fluorescence intensity
PBS = phosphate-buffered saline
PCI = percutaneous coronary intervention
PDE = phosphodiesterase
PSGL = P-selectin glycoprotein ligand

mediated platelet-leukocyte interactions would also suppress leukocyte Mac-1 expression that leads to the prevention of neointimal thickening and restenosis.

To confirm this hypothesis clinically, we measured the in vivo expression of Mac-1 on the surface of neutrophils, as well as that of P-selectin on the surface of platelets in patients undergoing coronary stenting, and we compared two post-stent antiplatelet regimens—cilostazol and ticlopidine. In addition, we also assessed cilostazol's direct action on neutrophil Mac-1 expression in an in vitro experiment.

## METHODS

**Study design.** The subjects included 70 consecutive patients with isolated atherosclerotic coronary artery disease of the proximal left anterior descending coronary artery who underwent initial elective single coronary stent implantation. The patients were randomly assigned to either a cilostazol or ticlopidine group at least three days before PCI. The patients assigned to each group started receiving daily oral cilostazol (200 mg) or ticlopidine (200 mg), both of which are standard doses in Japan, in addition to 81 mg aspirin three days before PCI, because ticlopidine requires two or three days to reach an effective blood concentration. Each specific antiplatelet regimen was continued until follow-up coronary angiography. Coronary stent implantation was performed using standard techniques with the femoral approach, and lesions were assessed by quantitative coronary angiography. Before PCI, a catheter was positioned in the coronary sinus and left for 48 h after the procedure. Coronary sinus blood was collected via the coronary sinus catheter before PCI and at 15 min, 24 h, and 48 h after coronary stenting. Whole blood was immediately collected into a tube containing acid citrate dextrose. The study protocol was approved by the local ethics committee, and written, informed consent was obtained from each patient.

**Expression of activation-dependent P-selectin on surface of platelets.** Flow cytometric analysis of the internal alpha-granule membrane protein P-selectin expressed on the surface of activated platelets was performed using phycoerythrin-labeled anti-CD62P (Immunotech, Eugene, Oregon). Isotype-, fluorochrome-, and protein concentration-matched controls were run in parallel for phycoerythrin-labeled immunoglobulin G (IgG1) (Dako Cytomation, Glostrup, Denmark). Immunofluorescence staining was performed using minor modifications of previously published procedures. Briefly, 100 $\mu$l of whole blood was first fixed in 1 ml of 1% paraformaldehyde for 2 h at 4°C. After centrifugation at 10,000 rpm for 1 min, the supernatant was removed, and the pellets were washed twice with 1 ml of phosphate-buffered saline (PBS), followed by centrifugation at 10,000 rpm for 1 min. The pellets were then suspended in 1 ml of PBS with 0.1% bovine serum albumin and 20 $\mu$l of each monoclonal antibody was added. After incubation in the dark for 15 min at room temperature, the samples were washed once more and suspended in 1 ml of PBS. A FACSCalibur laser flow cytometry system (BD Bioscience, San Jose, California) was used for flow cytometry and calibrated daily with a mixture of monosized, fluorescent beads (CaliBRITE, BD Bioscience). We analyzed scatter signals and fluorescence intensity. The light-scattering properties projected on a scattergram identified the platelet cluster. Fluorescence intensity was expressed on individual cytohistograms, with the region of interest limited to the platelet cluster. The mean channel fluorescence intensity (MFI) was calculated as an index of the expression of P-selectin.

**Expression of Mac-1 on surface of neutrophils in vivo.** The expression of the adhesion molecule, Mac-1, on the surface of neutrophils was analyzed in the same manner as previously described. Briefly, whole blood was immediately collected into a tube containing acid citrate dextrose. Immunofluorescence staining was performed using fluorescein isothiocyanate (FITC)-labeled anti-CD16b (1D3; Beckman Coulter, Fullerton, California) and phycoerythrin-labeled anti-CD11b (Leu 15; Becton Dickinson). Isotype controls were run in parallel for FITC-labeled IgG1 (BD Bioscience) and phycoerythrin-labeled IgG2a (BD Bioscience). After completion of hemolysis by the lysing solution, the white blood cell sediment was fixed in a paraformaldehyde solution with PBS. Flow cytometric analysis was then performed using the FACSCalibur laser flow cytometer. We could detect neutrophils as CD16b-positive cells. Expression of CD11b (Mac-1 specific alpha subunit) on the surface of neutrophils was detected as MFI of phycoerythrin fluorescence.

**In vitro assessment of cilostazol's direct action on neutrophil Mac-1.** Blood was collected from seven healthy volunteers with sodium citrate. After completion of hemolysis, the white blood cells were sedimented, rinsed, and suspended. Cilostazol was dissolved in dimethyl sulfoxide (DMSO), and 3, 10, and 30 $\mu$mol/l doses of cilostazol were co-incubated with the white blood cell suspension and stimulated with 0.05 $\mu$mol/l of formyl-methyonyl leucyl phenylalanine (FMLP) for 24 h. Both FITC-labeled anti-CD16b and phycoerythrin-labeled anti-CD11b were added to the white blood cell suspension and incubated. Neutrophils were detected as CD16b-positive cells using the FACSCalibur flow cytometer. Expression of CD11b on the

**Table 1.** Baseline Characteristics

| | Cilostazol Group (n = 34) | Ticlopidine Group (n = 32) | p Value |
|---|---|---|---|
| Age (yrs) | 62.8 ± 3.2 | 63.1 ± 2.3 | NS |
| Men/women | 20/14 | 21/11 | NS |
| Diagnosis (AP/OMI) | 18/16 | 17/15 | NS |
| Platelet count ($\times 10^4/\mu l$) | 25.6 ± 2.2 | 26.4 ± 2.6 | NS |
| Leukocyte count ($/\mu l$) | 5,870 ± 170 | 5,660 ± 190 | NS |
| Risk factors | | | |
| Family history, n (%) | 3 (9) | 3 (9) | NS |
| Smoking, n (%) | 27 (79) | 28 (88) | NS |
| Hypertension, n (%) | 14 (41) | 12 (38) | NS |
| Diabetes mellitus, n (%) | 5 (15) | 6 (19) | NS |
| LDL cholesterol (mg/dl) | 124 ± 5 | 122 ± 4 | NS |
| HDL cholesterol (mg/dl) | 38 ± 2 | 38 ± 3 | NS |
| Medications | | | |
| Nitrates | 32 (94) | 31 (97) | NS |
| Beta-blockers | 11 (32) | 10 (31) | NS |
| Calcium channel blocker | 9 (26) | 9 (28) | NS |
| Nicorandil | 2 (6) | 2 (6) | NS |
| Aspirin | 34 (100) | 32 (100) | NS |

AP = angina pectoris; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = not significant; OMI = old myocardial infarction.

surface of neutrophils was detected as MFI of phycoerythrin fluorescence.

**Statistical analysis.** Data are expressed as the mean value ± SD. A comparison of clinical variables between the two groups was performed using the Mann-Whitney *U* test for continuous variables and the chi-square test for categorical variables. Serial changes in the in vivo variables were evaluated by repeated measures analysis of variance with Dunnett's post-hoc test for intra- and inter-group comparisons. In vitro tests were analyzed by the nonparametric Friedman test. Correlations between two parameters were evaluated by simple linear regression. The p values of $<0.05$ were considered significant.

## RESULTS

**Coronary stenting.** Of a total 70 patients, 35 each were assigned to the cilostazol and ticlopidine groups, respectively. A total of four patients subsequently had to be excluded from analysis: a patient in the cilostazol group who underwent double stenting due to serious balloon-induced dissection occurring before stenting and three patients in the ticlopidine group who were obliged to discontinue its administration due to serious adverse events (liver dysfunction in two and granulocytopenia in one). Baseline characteristics were similar between the 34 patients in the cilostazol group and the 32 patients in the ticlopidine group who were included in the analysis (Table 1). Neither acute nor subacute stent thrombosis occurred in any patient in either group. No major cardiac events, major bleeding, or other serious complications were experienced in either group throughout the observation period. Quantitative coronary angiography results are shown in Table 2. At follow-up angiography, the minimal lumen diameter tended to be larger (2.48 ± 0.13 mm vs. 1.97 ± 0.15 mm, p = 0.052)

**Table 2.** Quantitative Coronary Angiographic Results

| | Cilostazol Group (n = 34) | Ticlopidine Group (n = 32) | p Value |
|---|---|---|---|
| Before PCI | | | |
| Lesion length (mm) | 10.2 ± 0.4 | 9.7 ± 0.5 | NS |
| Reference dimeter (mm) | 3.17 ± 0.11 | 3.14 ± 0.10 | NS |
| MLD (mm) | 1.02 ± 0.06 | 1.04 ± 0.05 | NS |
| Diameter stenosis (%) | 67.3 ± 1.8 | 66.9 ± 1.5 | NS |
| After PCI | | | |
| MLD (mm) | 2.82 ± 0.12 | 2.84 ± 0.11 | NS |
| Diameter stenosis (%) | 11.0 ± 0.8 | 20.1 ± 0.8 | NS |
| Acute gain (mm) | 1.80 ± 0.11 | 1.80 ± 0.09 | NS |
| Follow-up angiography | | | |
| MLD (mm) | 2.48 ± 0.13 | 1.97 ± 0.15 | 0.052 |
| Diameter stenosis (%) | 21.8 ± 3.6 | 37.2 ± 4.3 | 0.056 |
| Late lumen loss (mm) | 0.34 ± 0.07 | 0.87 ± 0.10 | 0.028 |
| Restenosis, n (%) | 4 (15) | 10 (31) | 0.048 |
| Target lesion revascularization, n (%) | 2 (6) | 8 (25) | 0.036 |

MLD = minimal lumen diameter; PCI = percutaneous coronary intervention.

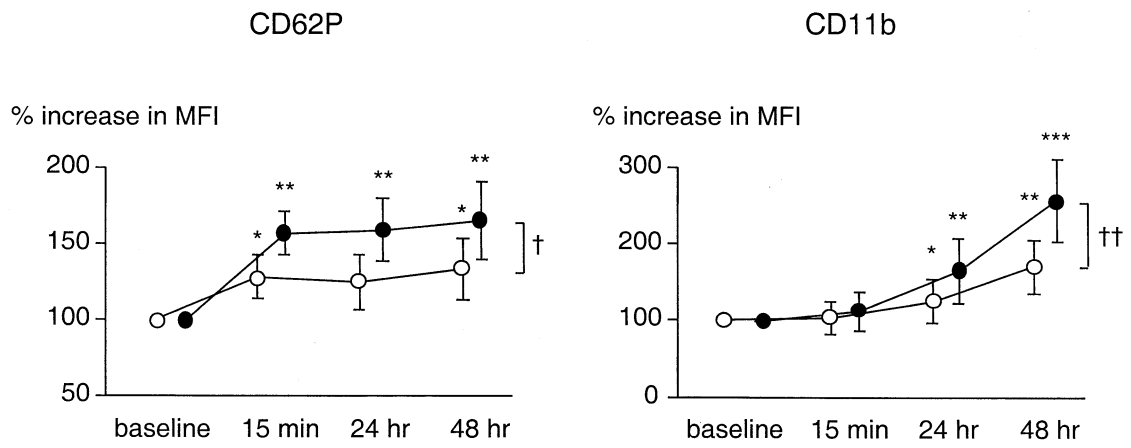


**Figure 1.** Serial changes in P-selectin (CD62P) on the surface of platelets **(left panel)** and Mac-1 (CD11b) on the surface of neutrophils **(right panel)** after coronary stenting. Platelet P-selectin and neutrophil Mac-1 increased after coronary stenting in a time-dependent manner, and the maximum increase was at 48 h. Both changes were suppressed in the cilostazol group compared with the ticlopidine group. *$p < 0.05$ vs. baseline. **$p < 0.01$ vs. baseline. ***$p < 0.001$ vs. baseline. †$p < 0.05$ for intergroup comparison. ††$p < 0.01$ for intergroup comparison. **Open circles** = cilostazol group (n = 34); **solid circles** = ticlopidine group (n = 32). MFI = mean channel fluorescence intensity.

and the late lumen loss (minimal lumen diameter after PCI minus minimal lumen diameter at follow-up angiography) was smaller (0.74 ± 0.34 mm vs. 1.12 ± 0.47 mm, $p < 0.05$) in the cilostazol group than in the ticlopidine group. As a result, the restenosis rate (15% vs. 31%, $p < 0.05$) and the target lesion revascularization rate (6% vs. 25%, $p < 0.05$) were lower in the cilostazol group.

**Changes in platelet P-selectin and neutrophil Mac-1 after stenting.** Expression of P-selectin on the surface of platelets increased after coronary stenting in a time-dependent manner, reaching a maximum value 48 h after stenting. These changes were lower in the cilostazol group than in the ticlopidine group, with the relative increases at 15 min, 24 h, and 48 h, as compared with the baseline values of 128 ± 14% vs. 161 ± 15%, 124 ± 18% vs. 163 ± 22%, and 133 ± 20% vs. 170 ± 27%, respectively ($p < 0.05$) (Fig. 1, left).

Serial changes in the expression of CD11b on the surface of neutrophils were also compared between the cilostazol and ticlopidine groups. Although no change was evident 15 min after stenting, the increase was noted after 24 h and maximally after 48 h in both groups. These changes were lower in the cilostazol group than in the ticlopidine group, with the relative increases at 15 min, 24 h, and 48 h, as compared with the baseline values of 103 ± 22% vs. 114 ± 26%, 125 ± 28% vs.170 ± 44%, and 170 ± 35% vs. 268 ± 58%, respectively ($p < 0.01$) (Fig. 1, right).

**Neointimal thickening and cell adhesion molecules.** Angiographic late lumen loss was correlated with relative changes in platelet P-selectin ($r = 0.27$, $p < 0.05$) and neutrophil CD11b ($r = 0.37$, $p < 0.01$) at 48 h after coronary stenting (Fig. 2).

**Cilostazol's direct action on neutrophil Mac-1 in vitro.** Cilostazol inhibited the expression of Mac-1 (CD11b) on the surface of neutrophils in vitro in a dose-dependent manner. The relative changes in CD11b expres-

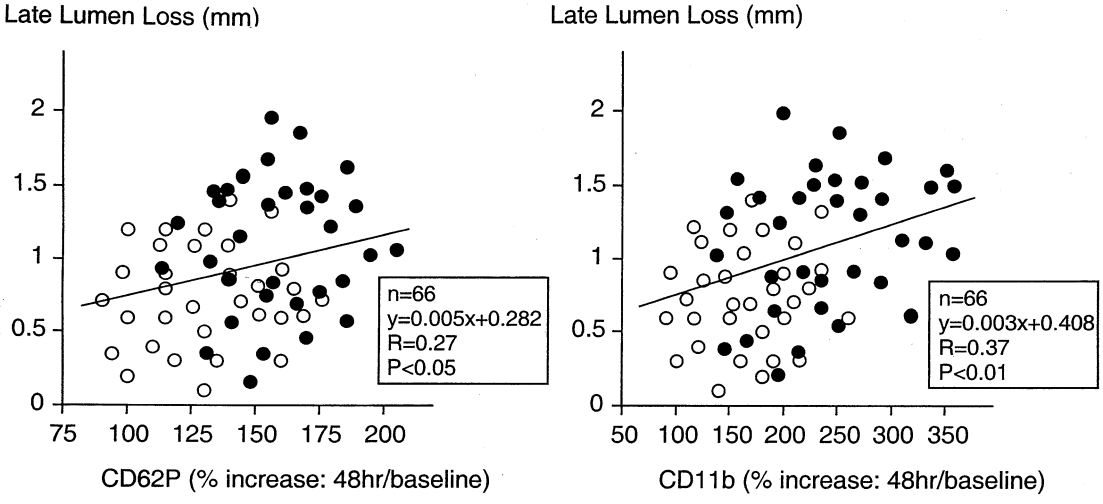


**Figure 2.** Correlation between angiographic late lumen loss and relative changes in platelet P-selectin **(left panel)** and neutrophil CD11b **(right panel)** at 48 h after coronary stenting. **Open circles** = cilostazol group (n = 34); **solid circles** = ticlopidine group (n = 32).

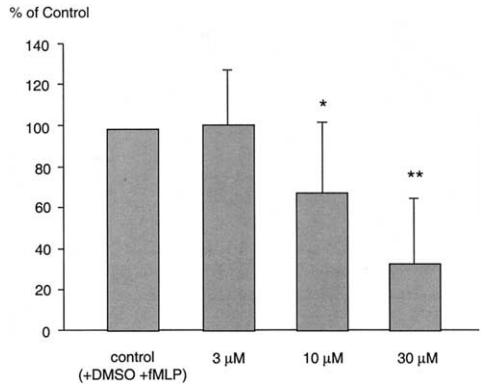


**Figure 3.** Cilostazol's direct action for Mac-1 (CD11b). Cilostazol inhibited an expression of Mac-1 on surface of neutrophils in vitro in a dose-dependent manner, compared with the control (+dimethyl sulfoxide [DMSO] +formyl-methyonyl leucyl phenylalanine [FMLP]). *$p < 0.05$. **$p < 0.01$.

sion at 3, 10, and 30 μmol/l of cilostazol versus control (+DMSO, +FMLP) were 102.2 ± 22.0%, 72.9 ± 29.0%, and 34.0 ± 27.3%, respectively (Fig. 3).

## DISCUSSION

In the present study, the expression of P-selectin on the surface of platelets increased immediately after coronary stenting with the increased expression continuing for 48 h after PCI. Also, the expression of CD11b increased (i.e., Mac-1 was upregulated) on the surface of neutrophils 24 to 48 h after PCI, with the maximum increase at 48 h. Moreover, angiographic late lumen loss (i.e., neointimal thickening) was correlated with relative changes in platelet P-selectin and neutrophil Mac-1 at 48 h after coronary stenting. In these findings, we observed the kinetics of cell adhesion molecules in the coronary sinus blood samples but not in the peripheral blood samples, so that we assessed local inflammation and cell activation in the PCI-injured coronary vessels, confirming our previous results. The increases in platelet P-selectin and neutrophil Mac-1 were lower in the cilostazol group than in the ticlopidine group. Additionally, the late lumen loss was smaller in the cilostazol group, correlating with both the kinetics of platelet P-selectin and neutrophil Mac-1. These results suggest the possibility that cilostazol has beneficial effects on restenosis reduction, presumably through inhibition of two cell adhesion molecules.

**Mechanisms of cilostazol's action.** Cilostazol acts as a selective inhibitor of PDE type III, an enzyme that breaks down cyclic adenosine monophosphate (cAMP). A higher level of cAMP stimulates the production of cAMP-dependent protein kinase, resulting in a lower level of intracellular $Ca^{++}$ within platelets, which, in turn, suppresses platelet activity (23). In addition to PDE III inhibition, we have observed a previous in vitro study that cilostazol inhibits an increase in P-selectin expression on the surface of adenosine diphosphate-stimulated platelets (2). Here we provide the first in vivo human data showing that cilostazol can inhibit stent-induced P-selectin expression on platelets, supporting the results of our previous in vitro experiments.

In the present study, we also demonstrated that cilostazol inhibited stent-induced Mac-1 upregulation on the surface of neutrophils. The activation of leukocytes, neutrophils, and monocytes is known to play an important causative role in the development of restenosis after PCI (7–10). Activated leukocytes transmigrate and infiltrate into the PCI-injured vessel wall and produce various cytokines, growth factors, free radicals, and proteolytic enzymes, leading to neointimal thickening and restenosis. At the PCI-injured vessel wall, which is denuded of vascular endothelial cells by the balloon inflation, platelets first adhere to the vessel surface and the platelet layer is formed. Leukocytes adhere to the platelet layer and then migrate into the vessel wall—namely, transplatelet leukocyte migration (18–20). In the process of transplatelet leukocyte migration, platelet surface P-selectin binds to P-selectin glycoprotein ligand (PSGL)-1 on the surface of leukocytes and mediates the rolling attachment of leukocytes with the platelet layer (21–22). In addition, subsequent firm adhesion of leukocytes is mediated by Mac-1, which is expressed on activated leukocytes and binds to ligands such as fibrinogen (20,21), platelet glycoprotein Ib alpha (24), intercellular adhesion molecule-2 (20), or junctional adhesion molecule-3 (25). Evangelista et al. (21,22) demonstrated in their in vitro experiment that the binding of P-selectin to PSGL-1 triggers tyrosine kinase-dependent signaling, which leads to functional upregulation or activation of Mac-1. Therefore, there is an important adhesion cascade between leukocytes and platelets, and cilostazol may block this cascade by acting on platelet P-selectin, as well as leukocyte Mac-1, to inhibit cross-talk between leukocytes and platelets. In this study, we focused on neutrophils but not monocytes based on our previous observations and the observations of others, that neutrophils are likely the first cells recruited to the injured vessel. Additionally, in the present study, we observed that cilostazol directly inhibited neutrophil surface Mac-1 upregulated in vitro by FMLP. The mechanism of cilostazol's direct inhibitory action for leukocyte Mac-1 is not well understood. Although cilostazol also has nonspecific inhibitory action for other PDEs in addition to PDE III, its inhibitory effect for PDE IV, which is known to be expressed in leukocytes, is very weak (26). Thus, we speculate that there are some unknown mechanisms independent of PDE inhibition. Our results suggest that cilostazol may inhibit Mac-1 both through a direct action as well as through inhibition of P-selectin and subsequent P-selectin–PSGL-1 signaling.

There is much evidence that Mac-1 is one of the key proteins in the mechanism of restenosis. We have demonstrated clinically that PCI induced activation (15) and upregulation (11–14) of Mac-1 on the surface of neutrophils and that Mac-1 kinetics were linked to angiographic late lumen loss—namely, neointimal thickening (13,14). Rogers

et al. (16) demonstrated in the rabbit iliac artery model that Mac-1 blockade by a monoclonal antibody against CD11b suppressed neointimal thickening after balloon-induced or stent-induced vessel wall injury. Simon et al. (17) demonstrated that, in Mac-1–deficient mice, neointimal thickening after balloon-induced carotid artery injury was suppressed compared with Wild-type mice. Therefore, chemical, biologic, or pharmacologic approaches targeting Mac-1 (i.e., Mac-1 blockade) are potentially powerful strategies for the prevention of restenosis.

Cilostazol also has direct inhibitory effects on smooth muscle cell growth and extracellular matrix synthesis through its PDE III-inhibiting action, which causes an increase of intracellular cAMP and a decrease of 3H-thymidine uptake (2,3). These effects possibly lead to direct inhibition of neointimal growth and a reduction in restenosis (4,27–29). In addition to the direct inhibition of neointimal growth through the action of PDE III, the results of the present study suggest that cilostazol may act as a Mac-1 blocker, and that this may play a role in the reduction of restenosis.

**Study limitations.** The present study had several potential limitations. In this study, we investigated the quantity of Mac-1 on the cell surface (upregulation), rather than functional Mac-1 activity using a Mac-1 activation-dependent antibody. In our previous study, we assessed the serial process of activation and upregulation of Mac-1 after PCI. Although activation of Mac-1 occurred earlier than its upregulation (15), we confirmed that serial changes in activation and upregulation were parallel and that the clinical significance of both findings was similar. Thus, this study only focused on the simple quantitative assessment of Mac-1. Although we assessed separately platelet P-selectin and leukocyte Mac-1 in this study, quantifying the number of platelet-leukocyte conjugates or the Mac-1 expression on platelet-bound and non–platelet-bound leukocytes might be of greater interest to further assess the adhesion cascade in the process of the platelet-leukocyte interaction with cross-talk between P-selectin and Mac-1 (30,31). This study compared cilostazol with ticlopidine, a therapeutic no longer in widespread use in the U.S. and European countries but a standard post-stent antiplatelet regimen in Japan. Recently, clopidogrel has replaced ticlopidine in Western countries (32,33). At present, however, clopidogrel is not available in Japan. The CREST (5) compared the cilostazol and placebo groups, both of which were under the baseline treatments with aspirin and clopidogrel and succeeded in the reduction of restenosis. Therefore, we can see that cilostazol prevents restenosis as an additional effect of clopidogrel.

**Clinical implications.** Although the biggest hurdle of PCI—restenosis—has been markedly reduced since the introduction of coronary stents, bare-metal stents cannot reduce restenosis to <20%. On the other hand, recent advances in drug-eluting stents, such as the Sirolimus-coated stent, have further reduced restenosis to <10% (34). Even with the drug-eluting stents, however, small vessel lesions and the complication of diabetes are still weakness for conquest of restenosis (35). Therefore, the problem of restenosis remains unresolved, and we should continue trying to reduce the restenosis rate until it is nearly equal to zero. The CREST (5) demonstrated by subgroup analysis that cilostazol was associated with a significantly lower restenosis rate, even in patients with small vessel lesions and in patients with diabetes. Therefore, oral cilostazol would be a powerful strategy for a further reduction of restenosis in addition to drug-eluting stents.

Recent chemical, biologic, or pharmacologic approaches to prevent restenosis are "anti-proliferative" or "anti-inflammatory" strategies. Cilostazol may represent a hybrid drug for the prevention of restenosis having both antiproliferative (PDE-mediated inhibition of smooth muscle cell proliferation), as well as anti-inflammatory (inhibition of leukocyte integrin Mac-1) effects.

**Conclusions.** Cilostazol may have effects for inhibiting Mac-1–mediated leukocyte activation directly or through P-selectin–mediated platelet activation, which may lead to a reduction in the rate of restenosis after coronary stent implantation.

## Acknowledgments

We acknowledge the technical support services of Ryoichi Sohma, BSc, Institute of Medical Science, Dokkyo University School of Medicine, and Toshiyasu Miyazaki, PhD, Hematologics Japan Co., Kawasaki, Japan, for flow cytometric analysis. We also thank Yukio Kimura, PhD, Thrombosis and Vascular Research Laboratory, Department of Advanced Pharmacology, Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan, for a critical review of this manuscript.

**Reprint requests and correspondence:** Dr. Teruo Inoue, Department of Cardiovascular and Renal Medicine, Saga University Faculty of Medicine, 5-1-1 Nabeshima, Saga 849-8501, Japan. E-mail: inouete@med.saga-uc.ac.jp.

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